Ronald Ross

RONALD ROSS AND THE PREVENTION OF MALARIAL FEVER

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ON Wednesday, December 10, 1902, at Stockholm, the Nobel prize for medicine, the second to be awarded, was bestowed upon Sir Ronald Ross for his demonstration of the transmission of malarial fever by mosquitoes. His immediate predecessor in the medical award was von Behring (1901), his successors were Finsen (1903), Pavloff (1904), Koch (1905), Golgi and Ramon y Cajal (1906), Laveran (1907), Metchnikoff and Ehrlich (1908), Kocher (1909), Kossel (1910), Gullstrand (1911), Carrel (1912), Charles Richet (1913), and Robert Bárány (1914). In this distinguished company it is noticeable that no less than three of the prizemen—Ross, Golgi, Laveran—were honored for their scientific work on the causation of malarial fever. To understand the significance of Ronald Ross's career, let us briefly consider the history of this disease.

Malarial fever has been known from the earliest times. It is well described in the medical writings of the ancient Greeks and Hindus. The intermittent forms, commonly known as quotidian, tertian and quartan, had already been differentiated by Hippocrates, who noted the principal symptoms, established a connection between the characteristic malarial enlargement of the spleen and marshy stagnant pools of water, and attributed the disease to the drinking of such water. Before the fifth century B.C., Greece was a mosquito-ridden country, but free from malaria. The disease was probably introduced by immigrants, as happened at Mauritius in 1866. After the age of Pericles, references to it became more extensive in literature, and the resulting rural depopulation had much to do with the downfall of Greece. The physicians of modern Greece have found the swamp fevers of their country to be not different from those described by Hippocrates in Thessaly and Thrace. One of them, Cardamatis, holds that some of the labors of Hercules symbolize the reclaiming of marshy areas from malarial fever, which he thinks identical with the "epiala" of the poets Theognis and Homer. The philosopher Empedocles (fifth century B.C.) was actually deified by the townsmen of Selinus for freeing the Sicilian city from malarial fever by draining the swamps in its vicinity. The Romans had a special goddess of fever (Mephitis), a bald, emaciated, dropsical figure who had a temple

on the Capitol, and whose very name suggests the swamps and their exhalations. The summer and autumn dangers of the Campagna were well known to the Roman satirists, Horace and Juvenal, who also mention the mosquito-net (*conopeum*). The close attention which the Roman architects paid to the construction of splendid aqueducts and drains shows their intuitive feeling about these things. A number of Roman writers on agriculture and architecture attributed malarial diseases to swamps, to the emanations from them, and to the small living creatures found in them. As these citations, first given by Lancisi, are always quoted in the original Latin, it may be well to translate them.

Varro (116–27 B.C.), writing on husbandry, says:

> It should be noticed whether any localities are marshy, for the same reasons, and because, when they dry up, certain minute animals are engendered, which the eyes can not see and which get into the body through the air by way of the mouth and nose, causing troublesome diseases.

Vitruvius, the architect (first century B.C.), says:

> The vicinity of a marsh is to be avoided, because, when the morning airs reach the house at sunrise, the mists of these places arrive with them, and the wind, mixed with these vapors, spreads the poisonous exhalations of the creatures inhabiting the marsh, and so makes the place pestilential.

Columella, the agriculturist (first century A.D.), says:

> Nor should buildings be erected near a marsh nor a military road adjoin it, because through heat it gives forth noxious poisons and engenders animals armed with dangerous stings, which fly at us in dense swarms.

Palladius says, in his poem on agriculture (fourth century A.D.):

> A marsh is by all means to be avoided, especially one lying to the east or west, and usually drying up in summer, because it engenders pestilence and harmful animals.

These extracts show that from the second century B.C. to the fourth century A.D. and after, the Romans had a clear notion of the relation between the fauna of marshes and malarial fever. The Hindus went even further. In the Susruta, a Sanskrit medical treatise which is at least 1,400 years old, the symptoms of malarial fever are clearly described and attributed to the bites of certain insects. Hints as to the connection between marshes and malarial fever will be found scattered through secular literature everywhere, for instance, in the dismal illustrations of the first edition of Mrs. Trollope's "Domestic Manners of the Americans," representing the ague-ridden inhabitants of the banks of the Mississippi, or in such a tale of the marshes as Baring-Gould's "Mehalah." Dr. Holmes, in "The Autocrat," likened the intermittent forms of malarial fever to certain short-lived insects—in that they "skip a day or two."

In 1618, the Countess Chinchon, wife of the viceroy of Peru, was healed of an intermittent fever by the use of cinchona bark, which was

introduced into Spain by her physician, Juan del Vigo, in 1640. The fact that cinchona, being a specific, not only cures malarial fever, but also differentiates it from other infections, gave a peculiar impetus to the study of the disease, which was carefully followed in England by Sydenham and Morton, in the seventeenth century, by Lind and Pringle, in the eighteenth century, and in Italy, by two great physicians, Lancisi and Torti. Lancisi, in 1717, published a large treatise on the noxious airs of swamps,[1] in which he revives views of the earlier Roman writers about the insects arising from them, in particular, the mosquitoes (*Culices*), of which he gives a naturalist's account, even suggesting their possible agency in inoculating disease. While he still held, in part, to the ancient doctrine of miasms or effluvia taken into the body *via* the respiratory and alimentary tracts, he was prone to regard these effluvia as organized or organic. The following luminous sentences, which have not been translated before, reveal the quality of his vision:

Cap. XVII., III. (p. 61): In a previous chapter, I have shown that mosquitoes (*Culices*) and other insects make their nests on the water during summer. It can therefore be easily seen that near swamps, where there are so many kinds of organisms and whence their multitudes are thrown into the surrounding air, the water, which the inhabitants use for drinking, is infected with these organisms.

Cap. XVIII., IX. (p. 66): Furthermore, no controversy can surely arise among professional men concerning the harmful effect which the insects of the swamps inflict upon us by mixing their noxious juices with their saliva and gastro-intestinal fluids. For, as I have shown above at length, their proboscis is always wet, and, as all their viscera are full of deleterious liquids, it is not possible that the juices rolling down with food and liquids into the stomach, are not there mixed with our ferments. . . . For this reason, we may conclude that marshy insects are highly injurious to the body of man by the inmixture of deadly juices as well as by the withdrawal of the useful ones which are in us.

Cap. XIX., III. (p. 72): Moreover, I take the rôle of a seer and not of a philosopher if I, without experiments, venture to affirm that, in camp fevers of this sort, the worms penetrate and ascend the blood vessels. For it would be necessary that the blood of those suffering from marsh fevers should be let, which medical reason seldom admits; and to carefully examine the blood with a microscope for insects of this kind, if such there be. But, although worms might be seen in the drawn blood, it would still be doubtful that these insects should be considered as the cause of the evil; or whether, which I consider more probable, it is the product of the breaking down of the fluids; whence all the minute ovules, after they have been wrapped up in particles of the blood, are set free or are supplied from the external air. I can therefore form no opinion from autopsies whether these diseases are carried by insects into the blood. Being rather content with a confession of my own ignorance, I must frankly concede that neither in abscesses due to nature or produced artificially in patients who frequently come from the neighboring swamps to Rome, nor in the examination of dead bodies, have I found insects in other viscera than the stomach and intestines, where they found room, quietude and food more easily than

[1] G. M. Lancisi, "De noxiis paludum effluviis eorumque remediis," Rome, 1717.

elsewhere. For the rest, through the supreme goodness of God, I have never been called upon to treat the plague, and, for this reason, I gladly refrain from expressing a definite opinion concerning pestiferous worms in the blood, as being a thing I know almost nothing about.

Lancisi also shows that good drainage drives away fevers. The great aqueducts and drains of the ancient Romans had apparently been designed for this purpose, and, through the Middle Ages up to the nineteenth century, the Papacy made many efforts to drain the Pontine Marshes and to cultivate the deserted Campagna, methods of sanitation which Ross summarizes as the "principle of mosquito reduction." Torti, at Modena, introduced cinchona bark into Italian practise, and by its use differentiated the pernicious forms, which do not yield to treatment, and of which he gave the classical account (1712). He also introduced the term "malaria," from the Italian *mal'aria* (bad air). The expressive term, first employed in English by John Macculloch, in his treatise "Malaria" (1827), epitomizes the earlier theory of its causation, viz., that it is due to miasms or effluvia, *i. e.*, gaseous emanations given off by stagnant water or even by the earth itself.

The next step in the history of malarial fever was the discovery of the parasites causing the disease. The theory that diseases may be caused by minute living organisms, invisible to the naked eye, is also very old, as is plain from the above citation from Varro. It was first stated in scientific form by Fracastorius, in his treatise on contagion (1546), and later by Athanasius Kircher (1658), who investigated minute organisms with the microscope. In 1730, as cited by Professor W. S. Thayer, Thomas Fuller, an English physician of the eighteenth century, made the following quaint suggestion that malarial fever may be caused by minute organisms:

Can any Man, can all the Men in the World, tho' assisted by Anatomy, Chymistry, and the best Glasses, pretend positively and certainly to tell us, what particles, how sized, figured, situated, mixed, moved, and how many of them are requisite to produce a quartan ague, and how they specifically differ from those of a tertian?

Agostino Bassi, who discovered the microorganisms causing silkworm disease, relates that the physician Rasori of Milan said to him of his discovery:

I am fully persuaded of the truth of your useful discovery. For many years I have held the opinion that the intermittent fevers are produced by parasites which call forth a new paroxysm by the act of their reproduction, which occurs at more or less rapid intervals according to the diverse species. In this way, the intermittent fevers, quotidian, tertian, quartan, arise (1846).

In the meantime, Jacob Henle had published his essay "On Miasms and Contagia" (1840), stating his theory of living contagia, with reference to Bassi's work; and, in 1849, Dr. John K. Mitchell published his treatise "On the Cryptogamous Origin of Malarious and Epidemic

Fevers," in which these diseases are attributed to minute fungi. This essay is a landmark in the history of the doctrine of contagion, but, for our purpose, the most important sentences in it are the following, referring to the causation of malarial fevers:

> Whatever may be their cause, it seems to have activity almost solely at night. *Darkness* appears to be essential to either its existence or its power.

Yet, strange to say, Mitchell, carried away by his theory of a fungous cause, says nothing whatever about mosquitoes, which were coming to be recognized more and more as agents in the production of both malarial and yellow fevers. In an old ordinance of Freetown, Sierra Leone, dated 1812, and cited by Kennan, the inhabitants (mostly freed slaves) are enjoined to keep the road in front of their plots in good condition in order to prevent the formation of "stagnant pools which generate disease and mosquitoes over the town" (Ross). In 1848, Dr. Josiah C. Nott, of Mobile, Alabama, advanced the provisional theory that yellow fever and malarial fever are of "probable insect or animalcular origin." It is sometimes asserted that Nott regarded the mosquito causation of malarial fever as proven. The only statement in his brilliant but rambling essay which suggests anything of the kind is the title of the paper itself, viz., "Yellow Fever contrasted with Bilious Fever—Reasons for believing it a disease sui generis. Its mode of Propagation—Remote Cause—Probable insect or animalcular origin, etc."[2]

The explanation of Nott's statement is simple. He got his theory of malaria, as every one else did, from Lancisi. In 1854, Louis Daniel Beauperthuy, a French physician residing in Venezuela, assigned a definite species of mosquito as the cause of yellow fever, holding that the poison is injected under the skin by the insect, as in snake bite. In 1866, Salisbury attributed the causation of malarial fever to spores of the vegetable family Palmella, and in 1879, Edwin Klebs and Tommasi-Crudeli announced the discovery of a *Bacillus malariæ,* neither of which availed as the true cause. The next few years witnessed a sudden leap in knowledge. On November 6, 1880, Alphonse Laveran, a French army surgeon, working at Constantine, Algeria, discovered the parasite of malarial fever, and in 1881, described three of its forms. In 1881 also, Dr. Carlos J. Finlay, after making a series of careful bionomic observations and some inoculation experiments, announced that yellow fever is transmitted *from man to man* by a special species of mosquito (*Stegomyia*[3] *calopus*), a theory which was to be proven in the most rigorous way by Major Walter Reed, of the U. S. Army Commission, and

[2] J. C. Nott, *New Orleans Med. and Surg. Jour.,* 1847–8, IV., 563–601. See on this point the essay of Dr. Juan Guiteras, "Insect-borne Diseases in Pan-America," Habana, 1915, p. 33.

[3] Finlay, *An. r. Acad. de cien. med. . . . de la Habana,* 1881–2, XVII., 147–169.

his associates, Carroll, Lazear and Agramonte, in 1900. Prior to Finlay however, Sir Patrick Manson had, in 1879, demonstrated that the mosquito transmits the disease produced by the parasite *Filaria*. In 1883, Dr. A. F. A. King, an English physician residing in Washington, D. C., gave nineteen cogent reasons why mosquitoes should transmit malarial fever and suggested screening the city from the marshy Potomac flats. In 1884, Carl Gerhardt demonstrated that malarial fever can be transmitted from the sick to the healthy by inoculation of the blood of the former,[4] in other words, as Ross says, "that the disease is not due to any gaseous emanation from the marshes, but is a true infection by some living virus." This laboratory demonstration of Gerhardt's may be said to have abolished the Miasm Theory of malarial fever. In 1885–6, Camillo Golgi,[5] at Pavia, showed that the Laveran parasites reproduce by formation of spores, and that the paroxysm of fever begins, as Rasori had surmised, just when the spores are liberated. That the parasites of the different forms of intermittent fever are different from each other and that similar parasites are found in birds was speedily shown by Marchiafava, Celli, Grassi and other Italian observers. In 1884, Laveran, and, about the same time, Koch, suggested that mosquitoes, as abounding in marshy places, may play the same part in malarial fever which Manson had shown them to play in filariasis. In 1894, Manson, in drawing a parallel between the malarial organism and *Filaria nocturna,* suggested that "the mosquito having been shown to be the agent by which the *Filaria* is removed from the human blood vessels, this, or a similar suctorial insect must be the agent which removes from the human blood vessels those forms of the malaria organism which are destined to continue the existence of this organism outside the body. It must, therefore, be in this or in a similar suctorial insect or insects that the first stages of the extra-corporeal life of a malarial organism are passed."[6] It is just at this point that the work of Ronald Ross looms large in importance.

Lieut.-Col. Sir Ronald Ross, K.C.B., F.R.S., the son of General Sir C. C. G. Ross, an eminent English soldier, was born on May 13, 1857, received his medical education at St. Bartholomew's Hospital, London, graduated in 1879, and entered the Indian Medical Service in 1881. He began to study malarial fevers in India in 1889. Doubting the truth of Laveran's discovery, he at first, after the fashion of Broussais, regarded the infection as the result of intestinal auto-intoxication. Being in London in 1894, he became acquainted with Manson's mosquito theory and upon returning to India the next year, undertook to verify

4 C. Gerhardt, "Ueber Intermittensimpfungen," *Ztschr. f. klin. Med.*, Berl., 1883–4, VII., 372–377.

5 C. Golgi, "Sull' infezione malarica," *Arch. per le sc. med.*, Torino, 1886, X., 109–135.

6 Manson, *Brit. Med. Jour.*, Lond., 1894, II., 1306.

it by experimental demonstrations. In 1895, he received the triennial Parkes Memorial Prize of 75 guineas and a gold medal for the best essay on "Malarial Fevers: their Cause and Prevention," Manson and Sir Almworth Wright being among the judges of the eleven essays presented. This essay simply summed up what he had learned from Manson.

Lancisi and his successors held that the malarial parasite or poison may somehow be carried from the marshes to man by mosquitoes. Manson, applying the analogy of his theory of the transmission of filariasis by the mosquito, thought that the insect carries the parasite from man to the marshes, laying her eggs on the surface of the water and dying in the act of doing so. He inferred that the embryos of the malarial parasite infect man by the digestive tract through the drinking of contaminated water. But long before Manson had taken up this hypothesis, it had been completely disproved by the Italians, Marchiafava (1885), Marino (1890) and Zeri (1890), whose careful experiments showed that it is impossible to infect healthy persons by the ingestion of water from the marshes. When Laveran investigated the malarial parasite in 1880, he found that certain large cells in the withdrawn blood give off long motile filaments, like the tentacles of the squid, which were supposed by Grassi, Bignami and other Italians to be the effect of the death agony of the parasite *in vitro*. Manson inferred that these filaments are in reality flagellate spores which escape from the parent parasites taken from the patient's blood by the mosquito and develop into the matured forms afterwards found in other malarial blood. So far, his theory explained how the parasites escape from the blood of an infected patient into the external world *via* the mosquito. But the important question was, how do they get into the body of a healthy patient and infect him with malarial fever? Ross soon found, like the Italians before him, that the hypothesis of the infection of the alimentary tract by drinking water falls to the ground completely. The real point of attack was obviously the motile filaments. He began his work at the malaria-ridden post of Secunderabad in 1895. In prosecuting his researches, he had first to devise methods for collecting, classifying, feeding, breeding and dissecting the mosquitoes themselves. He soon found that his Indian insects fall into three general classes, the brindled mosquitoes (*Stegomyia*), the gray (*Culex*) and the dappled or spotted-winged (*Anopheles*). He caused mosquitoes hatched from larvæ of these varieties to bite malarial patients and tried to find the parasites in the bodies of these insects, which were obviously free from malarial or other extraneous parasites of any kind. For two years, with constant improvement of technique, he labored at this problem without much success, his work being interrupted by a year and a half's detail to fight a cholera epidemic at Bangalore and by the Afridi War. At Bangalore, he made some inoculation experiments with mosquitoes upon Mr. Appia, assistant surgeon of the Bowring Civil

Hospital, and others, but without success. His natural inference was that either the disease is not inoculated by mosquito bites or that he had not got hold of the right kind of mosquito for the purpose. In April, 1896, he was sent to Ootacamund, a great hill station in the Nilgiri Hills, 8,000 feet above the sea level, and here among the tea and coffee plantations at the foot of the malarial Sigur Ghat, a trench-like hollow in the hills, he made his first step in advance, for here he found and began to concentrate his attention upon the dapple-winged *Anopheles* mosquito, which was to prove the true vector of the disease. Ordered back to Secunderabad in July, 1897, he repeated all his experiments upon the gray and brindled mosquitoes, without success, but did not get hold of any specimens of *Anopheles* until August 15. In the stomach of one of these, he found, on August 20, a delicate circular cell containing minute granules of a black substance like the melanin pigment, discovered by Meckel in 1847, which was shown by Virchow and Frerichs to be the essential pathological product of malarial fever, and is found in the malarial parasite. The next morning, he found in his eighth and last *Anopheles* similar bodies, only much larger.

> Both insects had been bred from larvæ in captivity; both had been fed for the first time on the same person—a case of malaria; no such objects as these pigmented cells—as I then called them—had ever before been seen in the hundreds of mosquitoes examined by me; the objects lay, not in the stomach cavity of the insect, but in the thickness of the stomach wall; all contained a number of black granules precisely similar in appearance to those contained by the parasites of malaria, and quite unlike anything which I had ever seen in any mosquito previously. Lastly these two mosquitoes were the first of the kind which I had ever tested. . . . These two observations solved the malaria problem. They did not complete the story, certainly; but they furnished the clue. At a stroke they gave both of the two unknown quantities—the kind of mosquito implicated and the position and appearance of the parasites within it. The great difficulty was really overcome; and all the multitude of important results which have since been obtained were obtained solely by the easy task of following this clue—a work for children.[7]

Shortly after confirming these results, Ross received peremptory orders to proceed to Kherwara in Rajputana, a petty non-malarial station, 1,000 miles distant, which he describes as "my Elba—almost my Île du Diable," for here his researches were interrupted until February, 1898, when he was given a six-months detail to investigate malaria and kala azar in Calcutta and Assam. In the meantime, W. G. MacCallum, at the Johns Hopkins Hospital, had discovered that the motile filaments of *Halteridium,* a parasite in birds, are agents in sexual conjugation, and in 1898, MacCallum and Eugene L. Opie demonstrated the same thing for the malarial parasite. Working with *Halteridium* and *Proteosoma,* both malarious parasites of birds, Ross proved at Calcutta on March 20, that *Proteosoma* can be transmitted from bird to bird by

[7] Ross, *Jour. Roy. Army Med. Corps,* Lond., 1905, IV., 551.

the gray mosquitoes (*Culex fatigans*), which, as he says, "practically proved the mosquito theory of malaria." He confirmed his results by a long series of differential experiments, which he transmitted to Laveran and Manson in letters of April 22, 1898, and after some interruptions, he discovered at Calcutta, on July 8, 1898, that the spores of the parasites were concentrated, not in the intestine, as he and Manson had supposed, but in what proved to be the *salivary gland* of the mosquito.

> The exact route of infection of this great disease, which annually slays its millions of human beings and keeps whole continents in darkness, was revealed. These minute spores enter the salivary gland of the mosquito, and pass with its poisonous saliva directly into the blood of men. Never in our dreams had we imagined so wonderful a tale as this.[8]

In confirmation of this, he infected a large number of sparrows with *Proteosoma* from gorged mosquitoes and his results were communicated by Manson to the British Medical Association in July, 1898. They attracted wide attention among the scientific experts but were absolutely ignored by the governmental and military authorities. Colonel Ross, his financial resources exhausted by these investigations, determined upon leaving India and returned to England in February, 1899. Shortly afterward, he was appointed first lecturer on tropical medicine at the newly created Liverpool School of Tropical Medicine, and here a new phase of his life work began.

In this year (1899), the Italians B. Grassi and A. Bignami gave conclusive evidence that the malarial parasites develop only in the *Anopheles* mosquito[9] and the causal relation was now definitely established. The next step lay in the direction of preventing the disease.

In August, 1899, Ross was sent out by the Liverpool school to investigate the West African coast fevers at Sierra Leone. Landing there on August 10, he soon found that two species of dapple-winged *Anopheles* (*A. costalis* and *A. funestus*) are the agents of transmission, and he immediately proceeded to establish for the first time the fundamental principles of the prevention of tropical malaria, viz., the culicidal treatment of the stagnant pools which were found to be the breeding places of *Anopheles*, scrupulous drainage of the soil, screening of buildings with wire gauze, isolation of the sick, and the habitual employment of mosquito nets and punkahs by individuals. In 1901, he fitted out another West African expedition to Lagos, which, owing to the unscientific, unpractical and unenthusiastic attitude of the government, was paid for by private philanthropy. At Lagos, the marshes were filled up with sand from the lagoons, wire netting for houses and cinchonization of individuals were instituted, and an annual subscription of £150 was obtained from the leading merchants for the organization of a mosquito brigade,

[8] Ross, *op. cit.*, p. 572.

[9] B. Grassi and A. Bignami, *Ann. d'ig. sper.*, Roma, 1899, N. S., IX., 258–264.

concerning which Ross wrote the first scientific treatise in 1902.[10] On the Gold Coast, in 1901, the streets were thoroughly drained, hollows in the ground were filled with rubble and earth, and all breeding places for mosquitoes were obliterated in 5,000 houses at Free Town. The British Bank of West Africa even opened a tropical sanitation fund. All this was accomplished through the propagandism of the Liverpool School of Tropical Medicine. But the crown of its achievement was to come at Ismailia, where, for the first time, assistance was obtained from the government itself. Ismailia, a sleepy, picturesque little town, on the shores of Lake Timsah, destined by De Lesseps to be the headquarters of the Suez Canal Company, was supplied with fresh water by a shallow canal from the Nile, built in 1877 and deepened for the passage of canal boats in 1882. This canal being further used to irrigate the desert and the outlying parks and gardens, much of the water ran to waste forming shallow marshes and ponds in and about the town.

> With the marshes came the mosquitoes; and with the mosquitoes came the fever, and with the fever came—the downfall.[11]

When malaria first appeared in 1877, there were 300 cases from August to December, out of a population of 10,000. By 1891, nearly 2,500 cases were reported and about 2,000 cases were treated annually. The town fell into decadence.

> Men, both Europeans and natives were unable to work, children were always ill, the death rate increased, while the birth rate fell. Every one was down with fever, and trade was soon at a standstill. The government offices were closed and were ultimately moved to Port Said.[12]

Ross arrived at the Suez Canal on September 12, 1902, in company with Sir William MacGregor, governor of Lagos, and immediately set about the task of mosquito reduction. The shallow pools and puddles the gardens and yards, and the cesspools under the houses were obliterated or treated with petroleum by the mosquito brigade, the marshes were drained, the canals and channels were cleared of reeds and other obstructions to flowing water, all water vessels, tubs and flower vases were emptied systematically, all breeding places of anophelines were visited and treated at stated intervals and penalties were imposed upon the townspeople who neglected to report faulty conditions. After an expenditure of 50,000 francs ($10,000), the anophelines were destroyed, and malaria disappeared, but an annual outlay of about $5,000 is necessary to keep the place healthy for "if the mosquito brigade stops work for a week, the mosquitoes return." The natives now call Ismailia "El turba e' nadeefa" (the clean tomb), because, like ancient Greece, it has never recovered from the blow dealt by malaria.

10 Ross, "Mosquito Brigades and How to Organize Them," London and New York, 1902.

11 Ross, "The Prevention of Malaria," Lond., 1910, p. 500.

12 *Op. cit.*, p. 500.

Similar results were obtained at Port Said, Cairo, Khartoum, in Italy and Greece, in the Federated Malay States, in the West Indies, Panama, and elsewhere. In 1906, at the request of the Lake Copais Company, Ross investigated malaria in Greece, where the language itself created a natural bar to statistical information. He found a valley population of two and a half millions with 250,000 cases and 1,760 deaths. In 1905, there were 960,000 cases and 5,916 deaths. The average number of cases throughout the kingdom was 29 per cent. The Anti-Malaria League, founded by Constantinos Savas in 1905, has gone far toward making the ultimate control of the disease possible. Equally effective was the work of Angelo Celli and the Italian Anti-Malaria Society begun in 1899. As Sir William Osler wrote to the *Times* in 1909:

> In Professor Celli's lecture-room hangs the mortality chart of Italy for the past twenty years. In 1887 malaria ranked with tuberculosis, pneumonia, and the intestinal disorders of children as one of the great infections, killing in that year 21,033 persons. The chart shows a gradual reduction in the deathrate, and in 1906, only 4,871 persons died of the disease, and in 1907, 4,160.

Robert Koch's work at Stephansort, New Guinea, in 1900, turned a hotbed of malaria into an absolutely healthy colony by the exclusive use of quinine and his methods were successfully applied in the other German possessions. One great discovery of Koch's was the extraordinary prevalence of tropical malaria in children, which enabled him to attack the disease almost at its source. In 1902–5, Captain Charles F. Craig showed that intra-corpuscular conjugation in the malarial plasmodia is the cause of latency and relapses of the disease, whence it was shown that malarial fever can be transmitted by human "carriers," apparently free from the disease themselves. The discovery of the rôle of the *Stegomyia* mosquito in the transmission of yellow fever by Carlos Finlay (1881) and its scientific demonstration by Reed, Carroll, Lazear and Agramonte in 1900, led to the elaborate and successful prophylactic measures by the United States Army in Cuba and Panama, which included of course the obliteration of malarial fever. A full account of anti-malarial work in all countries is given in "The Prevention of Malaria" (1910) by Ross and his colleagues.

To sum up Colonel Ross's achievement in the science of infection, he devised his own methods for collecting, classifying, feeding, breeding and dissecting the mosquitoes investigated by him, located the species *Anopheles* as the probable true vector of malarial fever, showed that the moonshaped variety of the malarial parasites is found in the body of the *Anopheles,* that the spores of the parasites are concentrated, not in the intestines, but in the salivary gland of the insect, and that analogous parasites may be transmitted from bird to bird by mosquitoes, thus making it possible for Grassi and Bignami to prove conclusively that the malarial parasites develop only in the *Anopheles* and that the disease is

transmitted by this mosquito from man to man. Having demonstrated this hypothesis by induction, he then proceeded to employ his theorem deductively, as applied science, with brilliant success, in the prevention and eradication of malarial fever in West and North Africa.

Colonel Ross kindly gives the following personal reminiscences [sent to Dr. Garrison after General Gorgas's departure for South America, June, 1916].

As every one knows, the Americans started their important sanitary work at Panama early in 1904 under the distinguished management of Colonel (now General) Gorgas, U. S. Army. He invited me, on behalf of the American government, to visit the Canal Zone in order to witness his measures, and as I was also asked to read a paper at the Congress of Arts and Sciences held in connection with the great Exposition at St. Louis, 19th–25th September, 1904, I determined to visit Panama after the Congress was over. At the end of the Congress, each of us who had read papers was given the sum of five hundred dollars to pay for our expenses in traveling over to St. Louis and returning, and we pouched this sum in notes with considerable satisfaction. Unfortunately many of us had scientific friends in the states, and I fell into the clutches of Dr. (now Sir William) Osler who swept me off to Baltimore. After a very warm time with him in that city, I fell into the hands of other friends who passed me on from Philadelphia to New York and left me so little leisure to spare from hospitality that I could not get my five hundred dollars banked or converted into an exchange note. I was then rushed on board ship where I met Colonel Gorgas himself (who was not going to Panama with me) and was duly photographed and speeded on my journey with the good wishes of my many friends. A week later, after a delightful voyage, I arrived in Colon with my five hundred dollar notes still in my pouch. We were immediately sent across the Isthmus and arrived at Panama the same evening. The weather was extremely hot, with the usual result on my nervous system that I became very sleepy and lazy. On arrival at Panama, I was ushered into the Medical Officers' Mess. Now this was a teetotal mess, and I am not a teetotaller by profession, though, I hope, always very moderate in my devotion to god Bacchus. They gave us beef-steak and iced water for dinner, and I became so extremely sleepy after this diet that when I went to my sleeping quarters in a house near the hospital, occupied by Captain Lyster, United States Army, I determined to go to bed at once (within my mosquito netting) and sleep off my fatigue. Lyster did the same thing and we slept beautifully all night. Unfortunately I was so overcome with the beaf-steak and the iced water that I left my pocket book containing my five hundred dollars on the table at the foot of my bed, though fortunately I kept my watch in the pocket of my sleeping jacket. There was a considerable wind all night which kept the doors slamming or creaking, and I was too indifferent to the world to care what happened. When we woke in the morning we were entirely refreshed and as strong as lions in consequence of the beef-steak; but Lyster ran in to my room with alarm written on his face. Sure enough my clothes had been thrown about the room in a terrible manner and my cigar case was found empty in the bathroom. He said that his best suit of blue serge clothes had unaccountably disappeared. We presently heard wailings from all round, and Dr. Balsch, the Health Officer of Panama rushed in from the next house to say that his valuable gold watch had gone. Then I bethought me of my five hundred dollars and ascertained that my pocket book had also disappeared entirely. The fact was that all our houses had been raided that night by an expert gang of house-breakers, who had taken my money and the numerous valuables from my friends.

I was not worried about my loss, because, fortunately, I had asked my agent in England to put a sum of money at my disposal in case of need with a New York bank. Hence, though my friends offered to give me any cash I liked, I refused their offers, and lived for a week in Panama entirely on hospitality with the assistance of a few dollars in my breeches' pocket. Really I was never more happy in my life, and felt the complete joy of being an absolute pauper. At the end of my visit I went on board the same ship, which was to take me back to New York. As I had no money on board the ship I remained equally happy during the voyage, but just as we reached New York my sole remaining hat was blown into the sea. I therefore arrived at New York on a Saturday, with one dollar in my pocket and no hat. Nevertheless I presented myself at the Waldorf-Astor Hotel and asked them to take me in on credit only till Monday. They lent me some cash to buy a hat and fed me as if I had not been a pauper at all. Next Monday my happiness ceased again, because the bank accepted my credit-note from London and filled my pockets with the detestable stuff on which we live.

I believe that none of us ever got back our losses, but the fun of the business repaid me. I believe that I was the only pauper who had ever been the guest of the Great American Republic.

I say nothing here of the extremely interesting time I had in Panama. My only grief was that Colonel Gorgas was not with me; but Captain Lyster, Dr. Balsch, Colonel Carter, Dr. Ross, Mr. Le Prince and every one else gave me the best time imaginable, but generally on a teetotal basis! I ascribe my loss entirely to the somnolence induced in me by teetotalling, and have abandoned that calling ever since.

The most bitter irony of the business was that, when I arrived in Liverpool, my friends there refused to believe that my five hundred dollars had been stolen at all and averred that it had all been thrown away in wild dissipation with Sir William Osler and other congenial friends, so that I obtained the reputation of being, not a teetotaller, but a wastrel.

RONALD ROSS

26th June, 1916.

Ronald Ross is a man of remarkable versatility. He is not only a parasitologist and sanitarian of proven abilities, but also a mathematician, a poet and a publicist. He is editor of *Science Progress,* and one of the editors of *Annals of Tropical Medicine.* In 1905, he introduced his method of solving equations by "operative division,"[13] a modification of that discovered by Michael Dary, a gunner of the tower of London, on August 15, 1674, and communicated by him in a letter to Newton on that day. The rationale of this method consists in expressing an algebraic operation as a "verb function," an action upon or arrangement of quantities, without stating the quantities themselves. It is thus one of the symbolic or substitution algebras which have played such a prominent rôle in modern mathematics. Ross defines an algebraic operation, some particular grouping or arrangement of quantities, as a verb, while a function, the result of such grouping, is definable as a substantive or noun. He holds that this notation gives the power of expressing any algebraic operation without reference to the quantities employed, *e. g.,* if *o* denote

[13] Ross, *Proc. Roy. Irish Acad.,* Dubl., 1905, XXV., Sect. *A,* No. 3, 31–76.

an operation as a verb function, then o^n will denote the operation of raising a quantity to the nth power, when $[o^n]x = x^n$, and since o^0 is unity, $[ao^0 + bo^1 + co^2]x = a + bx + cx^2$. In all this, Ross modestly regards himself as an amateur, but he believes that Newton himself may have adapted Dary's principle in devising his own method of obtaining the roots of equations by approximation. In Ross's operative division, each term of the quotient operates on the whole divisor instead of being multiplied into it, as in ordinary algebraic or arithmetical division. The rest of Ross's mathematical work has been concerned with "pathometry," a term of his invention signifying the quantitative study of parasitic invasion and infection in individuals or groups of individuals. He has investigated, for instance, the variations of mosquito-density in relation to time and place, the relation of mosquito output to extent of breeding surface and the relations of mosquito-density to the rate and extent of malaria-incidence in a given locality; also the relation of malaria-rate to such factors as parasite-rate, spleen-rate (number of malarial cases with enlarged spleen), fever-rate, and the proportion of people who are constantly ill from malarial fever, all of which are lessened by "mosquito reduction." This work on mosquito distribution is said to have been the inspiration of the mathematical memoir of Pearson and Blakeman on random migration. Latterly, Colonel Ross has occupied himself with the study of epidemic curves, that is, the graphs predicting the course and probable duration of an epidemic from its initial data, which were first investigated by the English statistician, Dr. William Farr, in 1866. Work of this kind has been attempted only within the last sixty years, the explanation being that there have been few vital and medical statistics covering large averages until recent times. In the eighteenth century, Daniel Bernouilli applied the calculus of probabilities to smallpox epidemics and got an equation giving the number of survivors who have not had the disease in terms of the number surviving at a given age out of a given number, the number attacked and the number not attacked in a year. The recent aim has been to discover the law of which an epidemic, in relation to space and time, is to be regarded as an expression. In other words, while the hygienist aims to influence and limit the course of the epidemic by such coefficients as vaccines, sera, destruction of insects or animals carrying the disease, or other aggressive sanitary measures, the aim of the modern epidemiologist is statistical prognosis or the prognosis of infectious disease on a grand scale. The strong point made by Farr was that the theoretical curve of an epidemic in space and time is a normal curve. The generic idea is that all recurrent natural phenomena, *e. g.*, the weekly ratio of illegitimacy to the normal birthrate in a large city, tend to acquire a certain uniformity. Farr's law states the general epidemiological principle that subsidence

along a definite line is a property of all zymotic diseases. During the cattle plague of 1865–6, Mr. Lowe in the House of Commons (1866), predicted an epizootic of tremendous proportions, with a formidable rate of increase. His views were controverted by Dr. William Farr in a letter to the *Daily News* of February 17, 1866,[14] in which it was maintained that the rate of increase would begin to decrease rapidly at a certain point, after which it would go on decreasing until the rate of incidence itself decreased. This generalization, the facts of which are not unlike the phenomena of depopulation in modern states, is known as Farr's law. It implies, as Farr says, that "the curve of an epidemic at first ascends rapidly, then slowly until it attains a maximum, then makes a turn and falls more rapidly than it mounted." To prove his case, Farr plotted a bell-shaped probability curve of the actual epidemic, based upon reported and calculated statistics, and predicted that it would have an early maximum with a rapid decline, ending in June, 1866. Actually, the epidemic rose to a maximum on February 24, a fortnight earlier than Farr had predicted, but subsided in the early summer, as he surmised, although at a slower rate than his curve indicated. Nevertheless, his calculations, in the face of the public alarm obtaining at the time, were a great advance in epidemiology, what Ross calls "the first *a posteriori* work on epidemics," in which it was attempted to work back inductively to underlying principles from observed and observable data. Farr also applied his principle with success to a subsequent smallpox epidemic. The cause of the constantly decreasing increase has been sought in the gradual lack of susceptible or infective material, *e. g.*, in the effects of vaccination on the Boston epidemic of smallpox in 1721, a view favored by Ross. Another cause, favored by Brownlee, is to be found in Pasteur's theory of attenuated viruses. Pasteur showed that the pathogenic properties of a virus may be increased or attenuated by successive passages through the bodies of appropriate animals, from which he reasoned that the origin or extinction of an epidemic disease may be due to the strengthening or weakening of a virus by environmental conditions, either in external nature or in the bodies of animals. This seems borne out by the thermodynamic conditions governing the virulence of microorganisms. In the bodies of bacillus carriers, the typhoid bacillus is temporarily inactive or inactivated, for the nonce, an insulated "adiabatic" system, in that energy can neither go in nor out of it. In the body of a susceptible person, the same bacillus becomes activated and pathogenic, whence it is reasoned that a nonvirulent strain of a bacillus may become pathogenic under certain conditions in nature. In this way, Sudhoff has attempted to explain the origin of syphilis in Europe. Prior to its appearance as such, in 1494, there had existed a class of lepra-like diseases yielding to mercury, as is shown by old Italian prescriptions of

[14] Reprinted by Brownlee in *Brit. M. J.*, Lond., 1915, II., 251.

1465. These diseases Sudhoff regards as foci of an endemic spirochetosis, which, in persons rendered weak and susceptible by wars, famine and debauchery, became a virulent infection. Sydenham saw European syphilis as a mode of West African yaws, and salvarsan is a true *therapia sterilisans* for the spirochete of yaws. Pasteur's law explains the facts about the great plague of London (1666). When the disease began to abate, vast numbers of people who had fled the city returned, and Pepys, in his "Diary," made anxious predictions as to a possible recrudescence of the epidemic. But this was not the case. The plague had worn itself out, and it is said that some even occupied the beds of plague patients with immunity.[15] Yet, while lack of susceptible persons and attenuation of the specific virus are not identical causes, they may sometimes amount to the same thing. Since Farr's time, mathematical investigations of epidemics have followed two main lines. Brownlee, Greenwood and other English statisticians have applied the skew curves, devised by Karl Pearson, to the analysis and gradation of the statistics of various epidemics, and Brownlee has found that most of the curves evolved are symmetrical bell-shaped curves of the Farr type, with the difference that the curves do not fall more rapidly than they rose, as in Farr's original hypothetical curve of 1866, but more slowly, as in the actual figures of his 1866 epidemic (Pearson's type IV. curve).

Ross's investigations have followed the lines laid down by himself in 1904, and his ultimate aim is to account, not only for the epidemics which have a symmetrical or normal curve, but also for the asymmetry which characterizes many epidemics influenced by external forces. He divides infectious diseases into three classes: "(1) diseases like leprosy or tuberculosis, which vary little from month to month, but may slowly increase or decrease in the course of years; (2) diseases like measles, scarlatina, malaria and dysentery, which are constantly present in many countries and flare up as epidemics at frequent intervals; and (3) diseases such as plague or cholera, which disappear entirely after periods of acute epidemicity." Concerning the diseases of the second class, he inquires whether they may be due to "a sudden and simultaneous increase of infectivity in the causative agents living in infected persons, or to changes of environment which favor their dissemination from person to person, or merely to the increase of susceptible material in a locality due to the gradual loss of acquired immunity in the population there." It is known, for instance, that measles has occurred at Perth regularly every sixteen months during the last forty years, with but two variations; in Glasgow, every fifteen and a half months up to 1800, and every twenty-four and a half months from 1855 on; while the London records of measles during 1840–1912, indicate a periodicity of about 1⅞ years.[16]

15 J. Brownlee, *Proc. Roy. Soc. Edinb.*, 1905–6, XXVI., 486.
16 *Brit. M. J.*, 1915, II., 652.

The coefficients which Ross introduces are the measures of variation due to mortality, natality, immigration and emigration of the non-affected and affected persons respectively. From a set of equations containing these coefficients, the total population and the ratio of the affected to all its members, he gets an equation giving the proportion of the total population affected at a given time.[17] The curve of which this equation is an expression is, in the simplest case, the regular bell-shaped curve, in other words, the assumption that the infectivity ratio is constant or proportional to the number of persons affected gives curves which are not irreconcilable with the hypothesis of decline from exhaustion of susceptible material, opposed by Brownlee. These studies in "à priori pathometry," still to be completed, give Ronald Ross a distinguished place in the modern English school of iatromathematicians.

In 1906, there appeared a little volume of verses with the title page "In Exile, by R. R. Privately Printed," of which the author says, in his preface,

> These verses were written in India between the years 1891 and 1899, as a means of relief after the daily labors of a long, scientific research.[18]

In a sympathetic review of this book, Dr. Weir Mitchell, a fellow medical poet, has said:

> In any climate and under the most indulgent conditions, what he did would have been remarkable. In India the lack of sympathy on the part of his military superiors, abrupt army orders, limited means and absence of help seemed ever ready at his happiest approach to success to mock him with delays. He must have felt as if, at times, some malign fate stood ready with obstacles over which no energy, no self-assurance of ultimate victory could prevail. I know of no medical story more interesting, no research which so surely found what it exacted, that heroism back of which lay energizing sense of duty. . . . Ronald Ross, when half blind or exhausted with work, turned to verse and sought in a difficult field for the relief that change of mental occupation affords, for the making of good verse is not an easy occupation, as several of the greatest poets have confessed. This little book is an interesting record of moods of mind, of hope, despair, sorrow and final triumph. It gives one a vivid conception of the effects of exile, personal losses and the torment of tropical conditions on a man with an imagination of high order, somewhat lacking for use in verse that which only much technical training can supply. There are many verses in this book which exacting self-criticism might have altered or left out. There are some easily amended defects of rhythm—verses which are needlessly obscure; but these concern me little. There are many quatrains of virile power, descriptions of eloquent force or notable passages of insight and deep feeling.[19]

Of Ronald Ross's poems, space permits the citation of but one, the

[17] Ross, *Proc. Roy. Soc. Lond.*, 1916, Ser. *A*, XCII., 207; 211 et seq.

[18] Colonel Ross has recently presented to the Surgeon General's Library his youthful dramas "Edgar" and "The Judgment of Tithonus" (Madras, 1883), "The Deformed Transformed," and the following books of original verses, viz., "Philosophies" (1909), "Fables" (1907), "Lyra Modulata" (1911) and "The Setting Sun" (1912).

[19] Mitchell, *Jour. Am. Med. Ass.*, Chicago, 1907, XLIX., 852.

verses written on the day upon which he discovered the malarial parasite in the body of the mosquito:

This day relenting God
  Hath placed within my hand
A wondrous thing; and God
  Be praised. At his command.

Seeking His secret deeds
  With tears and toiling breath
I find thy cunning seeds,
  O million-murdering Death.

I know this little thing
  A myriad men will save.
O Death, where is thy sting,
  Thy victory, O Grave!

Before Thy feet I fall,
  Lord, who made high my fate;
For in the mighty small
  Is shown the mighty great.

In his work as a sanitarian and eradicator of disease, Sir Ronald Ross has waged valiant and efficient warfare against the indifference and apathy of organized governments toward applied science, that medieval frame of mind so well described by Sir Clifford Allbutt:

> We find, in ruling classes, and in social circles which put on aristocratical fashions, that ideas, and especially scientific ideas, are held in sincere aversion and in simulated contempt.

Time and again has Ronald Ross returned to the charge in his general assault on unscientific administration in regard to the prophylaxis of infectious disease. His utterances on this theme reveal him as a publicist of large-minded type. Nothing seems more characteristic of the man than his general view of the whole matter:

> Probably few any longer accept the teaching of Hume, that the object of government is no other than "the distribution of justice." The function of an ideal civilized government might be described as the performance of all acts for the good of the public which individual members of the public are by themselves unable to perform—that is, the organization of public welfare. The individual can certainly add much by intelligence and virtue to his own welfare; but these qualities do not suffice to protect him altogether against those evils which can be combated only by concerted action, such as the depredations of disease and of external and internal human enemies; and where he is powerless, the government, and only the government, can help him. Now such concerted action is likely to be successful only when it is based on sufficient knowledge; and a scientific administration differs from an unscientific one just in this particular, that it seeks the necessary knowledge, while the other acts blindly. In nothing is this more manifestly the case than in connection with that department of public administration which is charged with the protection of the public against disease—a department second to none in importance, because it concerns not only our sentiments and our pockets, but our health and our lives.[20]

[20] Ross, *Nature*, Lond., 1907, LXXVI., 153.